Preventing Alzheimer’s disease and other dementias: present and future

Brain TLC--March 2016
Joseph Quinn, MD
Oregon Health and Science University
Portland VA Medical Center
Overview:

- Definition of terms:
- Preventing dementia at present: Life’s Simple 7
- Preventing dementia in the future: research progress report
- Preventing dementia in the future: the vision
- Preventing dementia in the future: invitation to volunteer
Overview:

Definition of terms:
– cognitive impairment, dementia, Alzheimer’s

• Preventing dementia at present: Life’s Simple 7
• Preventing dementia in the future: research progress report
• Preventing dementia in the future: the vision
• Preventing dementia in the future: invitation to volunteer
Some definitions:

• Dementia = any acquired brain condition that interferes with the ability to think and to carry out routine daily functions
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• “Mild cognitive impairment” = thinking impairment which is not as severe as dementia: does not interfere with everyday activities
Some definitions:

- Dementia = any acquired brain condition that interferes with the ability to think and to carry out routine daily functions.

Alzheimer’s disease = the most common cause of dementia, characterized by “plaques” and “tangles” in brain.
Some definitions:

- Dementia = any acquired brain condition that interferes with the ability to think and to carry out routine daily functions.

Alzheimer’s disease = the most common cause of dementia, characterized by “plaques” and “tangles” in brain.

![Amyloid Plaques](image1)

![Neurofibrillary Tangles](image2)

![Cerebral Atrophy](image3)
Some definitions:

- Dementia = any acquired brain condition that interferes with the ability to think and to carry out routine daily functions.

Alzheimer’s disease = the most common cause of dementia, characterized by “plaques” and “tangles” in brain.

Parkinson’s disease = A disease of movement With dementia occurring Years after diagnosis.
Some definitions:

- **Dementia** = any acquired brain condition that interferes with the ability to think and to carry out routine daily functions.

- **Alzheimer’s disease** = the most common cause of dementia, characterized by “plaques” and “tangles” in brain.

- **Parkinson’s disease** = A disease of movement with dementia occurring years after diagnosis.
Some definitions:

- Dementia = any acquired brain condition that interferes with the ability to think and to carry out routine daily functions

Alzheimer’s disease  
Parkinson’s disease with dementia  
Dementia due to strokes, etc
Overview:

• Definition of terms:
  Preventing dementia at present: Life’s Simple 7
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Brain Health recommendations from American Stroke Association

- www.AHA.org
- “Life’s simple 7”

“All the things that we know are bad for your heart turn out to be bad for your brain.”

Marilyn S. Albert, PhD
Johns Hopkins Medical Institutions
• American Heart / Stroke Association
  – Aerobic exercise
  – Control cholesterol
  – Eat according to AHA guidelines
  – Manage blood pressure
  – Lose weight
  – Reduce blood sugar
  – Stop smoking
• American Heart / Stroke Association
  – Aerobic exercise
  – Control cholesterol
  – Eat according to AHA guidelines
  – Manage blood pressure
  – Lose weight
  – Reduce blood sugar
  – Stop smoking

Only 2% of the American population meets all 7 guidelines.

(www.AHA.org)
Get Your Assessment

Life’s Simple 7™ Action Plan

This assessment test is based on the knowledge and expertise of The American Heart Association. Your assessment will help you understand what simple steps you may need to take to improve your heart health and quality of life. From there you will be directed to specific action plans that will help you get informed, change your behaviors and move you closer to your individual health goals.

It only takes about seven minutes and your results are completely confidential.

First Name

Email

Zip code

Country: USA

Resolution: Please select a resolution

Get your My Life Check Assessment

In just a few minutes with My Life Check, you can learn the state of your heart and what you can do to live a better life.
Get Active

Why Get Active?
We all know that exercise is good for us, but nearly 70% of Americans do not get the physical activity they need. Living an active life is one of the most rewarding gifts you can give yourself and those you love. Simply put, daily physical activity increases your length and quality of life. If you get at least 30 minutes of moderate physical activity each day (like brisk walking), five times per week, you can almost guarantee yourself a healthier and more satisfying life while lowering your risks for heart disease, stroke and diabetes. Parents, your children need 60 minutes a day—every day—so when you get active, you’re also modeling healthy living for the next generation.

The Price of Inactivity
If you exercise less than 150 minutes per week, you need to increase your activity level. Regular moderate intensity physical activity helps keep your heart in good condition. When you are inactive, you burn fewer calories, you are at higher risk for cholesterol problems, blood sugar and blood pressure problems, and your weight is often harder to manage. If that’s not enough, physically active people nearly always report better moods, less stress, more energy and a better outlook on life.

What Can I Do To Get Active?
- Make the time
  Nearly all of us feel time-crunchched and over-scheduled. And although anyone can fall into a busyness trap, only you can make your health a priority over life’s other demands. Even our nation’s President sets aside time to exercise. It can be done and only you can say ‘no’ to interruptions and ‘yes’ to your good health!

- Start with walking
  Walking is one of the best ways to get started. It’s easy, it’s social, it requires no special equipment, and it works! Just walk fast enough to get your heart rate up. Most of us can expect to cover 2 miles or more in a thirty minute block of time. If thirty minutes seems like an impossible goal, start with less. Some physical activity is always better than none! You can chart your progress as you work your way toward your goals.
Get Moving!
You’ll feel better and your health depends on it!

By exercising for as little as 30 minutes a day you can reduce your risk of heart disease. In fact, studies show that for every hour of walking, you may increase your life expectancy by two hours. The time to get moving is now! Start with a small goal and commit to it regularly. It won’t be long before you’re enjoying the benefits of an active life.

Learn More

Get Moving: Easy Tips to Get Active!

The Price of Inactivity
As adult and childhood obesity levels rise, so does the impact on our nation’s health.

American Heart Association Recommendations
Read the American Heart Association Recommendations for Physical Activity.
Get Walking Paths on the Go!

Now you can find and create Walking Paths from your phone! Download the American Heart Association’s My Heart. My Life.™ Walking Paths App for Android or iPhone today.

Learn more

Register Today!

Gain access to our suite of free tools that promote healthy living. Sign up for our resources and start seeing positive change today!

Register

My Walking Paths

Look for the Signs!
From parks to shopping malls, find — or create — American Heart Association-designated Walking Paths across the nation. Available via iPhone, iPad and Android, too! Get on the Path to Good Health

Activity Tracker

Keep an Eye on Your Routine
This amazing tool lets you log your activities, distance traveled and daily meals. See your progress and celebrate accomplishments! Use it today!

My Walking Plan

Get Your Personalized Walking Plan
Take this quick quiz to get your own personalized walking plan, developed by the American Council on Exercise (ACE) in collaboration with the AHA. Walk your way toward a healthier you!

Heart Walk

You Can Help Save Lives!
Designed to promote physical activity and heart-healthy living, the Heart Walk helps raise funds to fight heart disease and stroke in an environment that’s fun with friends, family and coworkers!

Learn More
AHA Diet recommendations

*Fruits and vegetables: At least 4.5 cups a day
Fish (preferably oily fish): At least two 3.5-ounce servings a week
Fiber-rich whole grains: At least three 1-ounce-equivalent servings a day
Sodium: Less than 1,500 mg a day
Sugar-sweetened beverages: No more than 450 calories (36 ounces) a week

• www.AHA.org
• “Life’s simple 7”
Fitness and cognition in the elderly
The Austrian Stroke Prevention Study

Neurology® 2016;86:418-424

Figure: Quartile analysis distribution of mass-specific $\dot{V}O_2$max, using quartile 1 as reference

$n=877$
55% women
Age 65±7 yrs
Diet: American Heart Association diet
Or Mediterranean diet
Life’s simple 7 and cognitive function:

The American Heart Association Life’s Simple 7 and Incident Cognitive Impairment: The REasons for Geographic And Racial Differences in Stroke (REGARDS) Study

Evan L. Thacker, PhD; Sarah R. Gillett, PhD; Virginia G. Wadley, PhD; Frederick W. Unverzagt, PhD; Suzanne E. Judd, PhD; Leslie A. McClure, PhD; Virginia J. Howard, PhD; Mary Cushman, MD, MSc

Table 1. Ideal, Intermediate, and Poor Levels of Life’s Simple 7 Components

<table>
<thead>
<tr>
<th>Component</th>
<th>Ideal (2 Points)</th>
<th>Intermediate (1 Point)</th>
<th>Poor (0 Points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>Never or former &gt;1 year</td>
<td>Former ≤1 year</td>
<td>Current</td>
</tr>
<tr>
<td>Healthy diet score*</td>
<td>4 to 5 points</td>
<td>2 to 3 points</td>
<td>0 to 1 points</td>
</tr>
<tr>
<td>Physical activity†</td>
<td>≥4 bouts per week of intense physical activity sufficient to work up a sweat</td>
<td>1 to 3 bouts per week of intense physical activity sufficient to work up a sweat</td>
<td>No intense physical activity sufficient to work up a sweat</td>
</tr>
<tr>
<td>Body mass index</td>
<td>&lt;25 kg/m²</td>
<td>25 to 29.9 kg/m²</td>
<td>≥30 kg/m²</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;120/&lt;80 mm Hg untreated</td>
<td>SBP 120 to 139 or DBP 80 to 89 mm Hg or treated to ideal level</td>
<td>SBP ≥140 or DBP ≥90 mm Hg</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>&lt;5.18 mmol/L (&lt;200 mg/dL) untreated</td>
<td>5.18 to 6.19 mmol/L (200 to 239 mg/dL) or treated to ideal level</td>
<td>≥6.22 mmol/L (≥240 mg/dL)</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>&lt;5.55 mmol/L (&lt;100 mg/dL) untreated</td>
<td>5.55 to 6.94 mmol/L (100 to 125 mg/dL) or treated to ideal level</td>
<td>≥6.99 mmol/L (≥126 mg/dL)</td>
</tr>
<tr>
<td>Life’s Simple 7 Score</td>
<td>Incident Cognitive Impairment Cases* N=573</td>
<td>Noncases** N=17 188</td>
<td>Standardized Percentage(^\d) (95% CI)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------------------------------------</td>
<td>----------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 6 points</td>
<td>241</td>
<td>5278</td>
<td>4.6 (4.0, 5.2)</td>
</tr>
<tr>
<td>7 to 8 points</td>
<td>175</td>
<td>6270</td>
<td>2.7 (2.3, 3.1)</td>
</tr>
<tr>
<td>9 to 14 points</td>
<td>156</td>
<td>5641</td>
<td>2.6 (2.1, 3.1)</td>
</tr>
</tbody>
</table>

[Diagram: Bar chart showing the standardized percentage of incident cognitive impairment across different health behavior scores.]
Cognitive health beyond “life’s simple 7”:

• Optimize sleep quality
  – Not refreshed upon awakening, snoring, stop breathing→ test for sleep apnea
  – Insomnia→ assess “sleep hygiene”, mood, anxiety, drugs (including caffeine and alcohol)
New research: Sleep may also help clear toxins from the brain

An artery in the brain of a mouse. The green shows cerebrospinal fluid in a channel along the outside of the artery. Photo courtesy of the University of Rochester Medical Center.

Cerebrospinal fluid (blue) flows through the brain and clears out toxins through a series of channels that expand during sleep. Image courtesy of Maiken Nedergaard.

Courtesy of Jeff Iliff, PhD, OHSU
Cognitive health beyond “life’s simple 7”: treat depression:

Depression damages brain cells:

- **Control**
- **Chronic Stress**

**Apical:**
- 20% length
- 16% spine density
- 10% spine size (fewer mature spines)

**Basal:**
- 10% spine size (fewer mature spines)
Depression is treatable!

- Improve quality of life
- Improve sleep, appetite
- Reduce risk of hippocampal damage and memory impairment from chronic stress
Cognitive health beyond “life’s simple 7”:
Mental exercise

• Does it generalize to other cognitive areas or to day-to-day function?
• Challenging to prescribe.
• But probably can’t hurt...
Mental exercise

• If you’re experiencing cognitive decline:
  – Some speech pathologists and OTs will do cognitive training/rehab.

• For prevention of cognitive decline:
  – Recommend activities that you are likely to stay with—hobbies, games, languages, music

• Also many options on line:
  – www.sharpbrains.org
  – Lumosity
Overview:

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“harnessing” immune system in human beings:
Brain amyloid can now be visualized in living patients:

Antibody therapy evaluated with amyloid imaging:

Figure 2: Estimated change from baseline over time in mean $^{11}$C-PiB PET
Data are least squares means and 95% CIs. *Difference between patients in the placebo group and those in the bapineuzumab group at week 78 = -0.24 (p=0.003). PiB=Pittsburgh compound B.
What we’ve learned:

• Immunotherapy can actually remove “bad” amyloid from the brain.
• But this treatment is not effective if started too late in the process.

• So we need to start “earlier”……..how do we identify and monitor the disease process if there are no symptoms?
Central dogma of biology:
The new biology of microRNAs:
EXOSOME BASICS
Exosomes are small membrane vesicles secreted by most cell types. Internal vesicles form by the inward budding of cellular compartments known as multivesicular endosomes (MVE). When MVE fuse with the plasma membrane, these internal vesicles are released as exosomes, which can travel to distant tissues to influence various aspects of cell behavior and physiology.

FROM FORMATION TO TARGET
In the first step of exosome formation, MVE bud inward to form small internal vesicles containing proteins, mRNAs, and miRNAs from the cytoplasm 1. These internal vesicles are released as exosomes when MVE fuse with the cell membrane 2. Alternatively, MVE can fuse with lysosomes, which degrade MVE contents 3. Upon reaching their destinations, usually determined by the binding of specific ligands on their surfaces, exosomes can enter target cells in one of two ways: by being taken up by the target cell's endocytic pathway 4 or by fusing to the target cell's membrane and releasing its contents directly into the cytoplasm 5. Cells also secrete other membrane-derived vesicles, such as ectosomes, shed vesicles, or microvesicles, which bud directly from the cell's plasma membrane 6. These vesicles are also known to carry active proteins and RNAs, as well as some compounds never before described in exosomes, but little is known about their effects on distant tissues.
Extracellular RNA Communication Program

commonfund.nih.gov/Exrna/index
## Extracellular RNA Communication Consortium

### Data Management and Resource Repository (DMRR) on Extracellular RNA (U54) RFA-RM-12-010

**MILOSAVLJEVIC, ALEKSANDAR**  
**BAYLOR COLLEGE OF MEDICINE**  
Data management and Resource Repository for the exRNA Atlas

### Extracellular RNA Biogenesis, Biodistribution, Uptake, and Effector Function (U19) RFA-RM-12-012

**BLELOCH, ROBERT H**  
**UNIVERSITY OF CALIFORNIA-SAN FRANCISCO**  
In Vivo Regulated Release and Function of Extracellular Small RNAs

**BREAKEFIELD, XANDRA OWENS**  
**MASSACHUSETTS GENERAL HOSP**  
exRNA released by glioblastoma alters brain microenvironment

**COFFEY, ROBERT J**  
**VANDERBILT UNIVERSITY MED CTR**  
Secreted RNA during CRC progression biogenesis function and clinical markers

**MCMANUS, MICHAEL T**  
**UNIVERSITY OF CALIFORNIA-SAN FRANCISCO**  
Genetic models for exRNA communication

**TUSCHL, THOMAS**  
**ROCKEFELLER UNIVERSITY**  
Definition of Serum Ribonucleoprotein Composition and its Regulation and Function

### Clinical Utility of Extracellular RNA for Biomarker Development (UH2/UH3) RFA-RM-12-013

**CARTER, BOB S**  
**UNIVERSITY OF CALIFORNIA SAN DIEGO**  
exRNA Biomarkers for Human Glioma

**DAS, SAUMYA**  
**BETH ISRAEL DEACONESS MEDICAL CENTER**  
Plasma miRNA predictors of adverse mechanical and electrical remodeling after MI

**FREEDMAN, JANE E,**  
**UNIV OF MASSACHUSETTS MED SCH WORCESTER**  
Extracellular RNAs: Biomarkers for Cardiovascular Risk and Disease

**HUENTELMAN, MATTHEW J**  
**TRANSLATIONAL GENOMICS RESEARCH INST**  
exRNA signatures Predict Outcomes after brain injury

**LAURENT, LOUISE C**  
**UNIVERSITY OF CALIFORNIA SAN DIEGO**  
ExRNAs for Early Identification of Pregnancies at Risk for Placental Dysfunction

**PATEL, TUSHAR**  
**MAYO CLINIC JACKSONVILLE**  
Extracellular non-coding RNA biomarkers of hepatocellular cancer

**SAUGSTAD, JULIE ANNE**  
**OREGON HEALTH AND SCI UNIVERSITY**  
Clinical Utility of MicroRNAs as Diagnostic Biomarkers of Alzheimers Disease

**TUSCHL, THOMAS**  
**ROCKEFELLER UNIVERSITY**  
Clinical utility of extracellular RNA as marker of kidney disease progression

**WEINER, HOWARD L**  
**BRIGHAM AND WOMEN'S HOSPITAL**  
Circulating MicroRNAs as Disease Biomarkers in Multiple Sclerosis

**WONG, DAVID T**  
**UNIVERSITY OF CALIFORNIA LOS ANGELES**  
Clinical Utility of Salivary ExRNA Biomarkers for Gastric Cancer Detection

### Clinical Utility of Extracellular RNA for Therapy Development (UH2/UH3) RFA-RM-12-014

**ABDEL-MAGEED, ASIM B**  
**TULANE UNIVERSITY OF LOUISIANA**  
Targeting Tumor-Derived exRNA-Containing Microvesicles by High Throughput Screening

**ARONIN, NEIL**  
**UNIV OF MASSACHUSETTS MED SCH WORCESTER**  
Exosome based therapeutics in Huntingtons disease

**KRAIG, RICHARD P**  
**UNIVERSITY OF CHICAGO**  
Exosome RNA

**MATIN, AC**  
**STANFORD UNIVERSITY**  
HER2-targeted exosomal delivery of therapeutic mRNA for enzyme pro-drug therapy

**QUESENBERY, PETER J**  
**RHODE ISLAND HOSPITAL**  
Regulation of renal and bone marrow injury by extracellular vesicle non-coding RN

**SCHMITTGEN, THOMAS D**  
**OHIO STATE UNIVERSITY**  
Targeted delivery of microRNA-loaded microvesicle for cancer therapy

**SOOD, ANIL K**  
**MD ANDERSON CANCER CTR**  
Novel extra cellular RNA-based combinatorial RNA inhibition therapy

**ZHANG, HUANG-GE**  
**UNIVERSITY OF LOUISVILLE**  
Fruit exosome-like particles for therapeutic delivery of extracellular miRNAs
“Clinical utility of microRNAs as diagnostic biomarkers of Alzheimer’s disease”
Obtain Clinically Characterized Human CSF Samples from the Oregon Alzheimer's Disease Center
Transfer Assigned CSF Samples to Jay Phillips

Isolate and Characterize Total RNA from CSF
Perform TaqMan Low-Density Array (TLDA) Analysis on CSF RNA
Transfer Data from QuantStudio to Theresa Lusardi

Perform Human miRNA Array Data Analysis for Ct and ΔCt

Perform Statistical Analysis of Human miRNA Array Data
Identify High-Priority miRNA Candidates
Correlate Candidate miRNAs with Clinical Characteristics
**Final UH3 miRNA Donor Table – Complete**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>AD</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
<td>30</td>
<td>53</td>
</tr>
<tr>
<td>Female</td>
<td>26</td>
<td>20</td>
<td>46</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>50</td>
<td>99</td>
</tr>
<tr>
<td><strong>Mean +/- SD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at LP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>69.61 +/- 9.82</td>
<td>68.7 +/- 7.49</td>
<td>69.09 +/- 8.5</td>
</tr>
<tr>
<td>Female</td>
<td>66.15 +/- 8.94</td>
<td>70.75 +/- 6.94</td>
<td>68.15 +/- 8.37</td>
</tr>
<tr>
<td>Total</td>
<td>67.78 +/- 9.43</td>
<td>69.52 +/- 7.27</td>
<td>68.66 +/- 8.41</td>
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<tr>
<td>MMSE at LP</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>28.83 +/- 1.64</td>
<td>18.23 +/- 6.71</td>
<td>22.83 +/- 7.37</td>
</tr>
<tr>
<td>Female</td>
<td>29.58 +/- 0.7</td>
<td>18.35 +/- 6.08</td>
<td>24.7 +/- 6.9</td>
</tr>
<tr>
<td>Total</td>
<td>29.22 +/- 1.28</td>
<td>18.28 +/- 6.4</td>
<td>23.7 +/- 7.18</td>
</tr>
</tbody>
</table>

**several microRNAs identified as markers of AD**

**Confirmatory studies under way at present**
Dementia prevention research progress report

- Antibody therapy for Alzheimer’s
- microRNA biomarkers for Alzheimer’s
Dementia prevention research progress report

• Antibody therapy for Alzheimer’s
• microRNA biomarkers for Alzheimer’s
• What about other dementia? Dementia in Parkinson’s?
“PANUC” is an NIH funded study to understand Cognitive decline and dementia in Parkinson’s
CONCLUSIONS AND RELEVANCE  Our data indicate that the APOE ε4 allele is an important predictor of cognitive function in PD across multiple domains. Among PD patients without dementia, the APOE ε4 allele was only associated with lower performance on word list learning and semantic verbal fluency, a pattern more typical of the cognitive deficits seen in early Alzheimer disease than PD.
Cognitive Profile of *LRRK2*-Related Parkinson’s Disease

Sindhu Srivatsal, MD, MPH, Brenna Cholerton, PhD, James B. Leverenz, MD, Zbigniew K. Wszolek, MD, Ryan J. Uitti, MD, Dennis W. Dickson, MD

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Non-Mutation Carriers</th>
<th>Mutation Carriers</th>
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</thead>
<tbody>
<tr>
<td>MDS-UPDRS III</td>
<td>1,153  28</td>
<td>28.64 (12.9) 3-79</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23.54 (9.1) 3-43</td>
</tr>
<tr>
<td>Cognitive status</td>
<td>1,057  25</td>
<td>210 (19.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (4.0) Dementia</td>
</tr>
</tbody>
</table>

N (%)
GBA Variants Are Associated With a Distinct Pattern of Cognitive Deficits in Parkinson’s Disease

Ignacio F. Mata, PhD,1,2 James B. Leverenz, MD,3 Daniel Weintraub, MD,4,5,6 John Q. Trojanowski, MD, PhD,7,8 Alice Chen-Plotkin, MD,4 Vivianna M. Van Deerlin, MD, PhD,7 Beate Ritz, MD, PhD,9,10,11 Rebecca Rausch, PhD,11 Stewart A. Factor, DO,12 Cathy Wood-Siverio, MS,12 Joseph F. Quinn, MD,13,14 Kathryn A. Chung, MD,13,14 Amie L. Peterson-Hiller, MD,13,14 Jennifer G. Goldman, MD, MS,15 Glenn T. Stebbins, PhD,15 Bryan Bernard, PhD,15 Alberto J. Espay, MD,16 Fredy J. Revilla, MD,16,17 Johnna Devoto, PsyD,16 Liana S. Rosenthal, MD,18 Ted M. Dawson, MD, PhD,18,19,20 Marilyn S. Albert, PhD,18 Debby Tsuang, MD, MSc,1,21 Haley Huston, BS,1,2 Dora Yearout, BS,1,2 Shu-Ching Hu, MD, PhD,1,2 Brenna A. Cholerton, PhD,1,21 Thomas J. Montine, MD, PhD,22 Karen L. Edwards, PhD,23 and Cyrus P. Zabetian, MD, MS1,2*

TABLE 4. Comparison of clinical characteristics across GBA groups

<table>
<thead>
<tr>
<th></th>
<th>Age at Onseta, y</th>
<th>MDS-UPDRS IIIb</th>
<th>Dementia</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean (SD)</td>
<td>Pc</td>
</tr>
<tr>
<td>Noncarriers</td>
<td>1,055</td>
<td>59.7 (10.5)</td>
<td>—</td>
</tr>
<tr>
<td>Mutation carriers</td>
<td>56</td>
<td>54.3 (8.7)</td>
<td>1.6 × 10−4</td>
</tr>
<tr>
<td>E326K carriers</td>
<td>54</td>
<td>57.3 (12.3)</td>
<td>0.22</td>
</tr>
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</table>
Genetics of cognitive decline in Parkinson’s disease:

• Some genes are “protective”, some promote dementia.

• The genetic basis varies from one individual to the next.
Genetics of cognitive decline in Parkinson’s disease:

• Some genes are “protective”, some promote dementia.

• The genetic basis varies from one individual to the next.

• Suggests we need to tailor our therapies to the individual: “personalized medicine” or “precision medicine”
Overview:

• Definition of terms:
• Preventing dementia at present: Life’s Simple 7
• Preventing dementia in the future: research progress report

Preventing dementia in the future: the vision

• Preventing dementia in the future: invitation to volunteer
## RESEARCH

### Precision Medicine

**Clarity for the Complexity of Dementia**

Brenna Cholerton, Eric B. Larson, Joseph F. Quinn, Cyrus P. Zabetian, Ignacio F. Mata, C. Dirk Keene, Margaret Flanagan, Paul K. Crane, Thomas J. Grabowski, Kathleen S. Montine, and Thomas J. Montine

<table>
<thead>
<tr>
<th>Population of Individuals</th>
<th>Traditional Approach</th>
<th>Precision Medicine Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classify by Risk</td>
<td><img src="image1" alt="Illustration" /></td>
<td><img src="image2" alt="Illustration" /></td>
</tr>
<tr>
<td>Surveillance for Preclinical Disease</td>
<td><img src="image3" alt="Illustration" /></td>
<td><img src="image4" alt="Illustration" /></td>
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<tr>
<td>Signs or Symptoms</td>
<td><img src="image5" alt="Illustration" /></td>
<td><img src="image6" alt="Illustration" /></td>
</tr>
<tr>
<td>Treat with</td>
<td>“One Size Fits All” Leads to Overall Mixed Results</td>
<td>Focus Existing, Repurpose FDA Approval, Invent New</td>
</tr>
<tr>
<td>Strategy</td>
<td><img src="image7" alt="Illustration" /></td>
<td><img src="image8" alt="Illustration" /></td>
</tr>
<tr>
<td>Outcome</td>
<td>Benefit, No Effect, Adverse</td>
<td>Benefit, Benefit, Benefit</td>
</tr>
</tbody>
</table>

[CrossMark](#)
Developing new treatments:

- "discovery" In vitro models
- Animal models
- Proof of concept trials
- Confirmatory clinical trials
- Personalized medicine
Genetically screen patients at risk of dementia.

Genetically screen family members.

Create genetically discrete cohorts for testing "personalized medicine":

- Treatment A: Small molecule
- Treatment B: Gene therapy
- Treatment C: Immunotherapy
- Treatment D: Stem cells
Dementia prevention clinic?

- Self-referred patients at risk of dementia (family history of dementia, prior stroke, Parkinson’s disease, head injury)
  - **Billable services:**
    - Cognitive assessment and risk factor assessment
    - Sleep medicine referral if appropriate
    - Life’s simple 7 group instruction or personalized health coach
  - **Billable vs research:**
    - Genetic counseling / testing
    - Brain imaging
  - **Research:**
    - Invitation to participate in registry or in specific studies
Overview:

• Definition of terms:
• Preventing dementia at present: Life’s Simple 7
• Preventing dementia in the future: research progress report
• Preventing dementia in the future: the vision
  Preventing dementia in the future: invitation to volunteer
Research registries:

• NeuroNEXT registry: all dementias and other neurologic diseases

• Alzheimer’s: www.alzactnow.org
Research volunteer opportunities:

• Antibody treatment to prevent dementia
• CSF microRNA study
• Parkinson’s dementia study
Research volunteer opportunities:

• Antibody treatment to prevent dementia
  – “A4 study” needs healthy volunteers over age 65
  – “Eisai” study needs MCI / early AD over age 50
  – Both studies involve IV infusions for 2-3 years

• CSF microRNA study
  – Needs healthy volunteers over age 50

• Parkinson’s and cognition study
  – -needs healthy volunteers over age 50 as control subjects
Research volunteer opportunities:

- ADresearch@ohsu.edu
- 503-494-7647
Thank you for your attention... Questions?